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(54) Title: SULFONAMIDE DERIVATIVE AS FACTOR XA INHIBITOR

(57) Abstract: The invention relates to 4-{4-[4-(5-chloroindol-2-ylsulfonyl)piperazine-1-carbonyl]phenyl}pyridine-1-oxide, or pharmaceutically-acceptable salts thereof or a solvate of either thereof, which possesses antithrombotic and anticoagulant properties and is accordingly useful in methods of treatment of humans or animals. The invention also relates to pharmaceutical compositions containing the above compound or a pharmaceutically-acceptable salt thereof.

SULFONAMIDE DERIVATIVE AS FACTOR XA INHIBITOR

The invention relates to 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl]phenyl}pyridine-1-oxide, or pharmaceutically-acceptable salts thereof or a solvate of either thereof, which possesses antithrombotic and anticoagulant properties and is accordingly useful in methods of treatment of humans or animals. The invention also relates to pharmaceutical compositions containing the above compound or a pharmaceutically-acceptable salt thereof.

The antithrombotic and anticoagulant effect produced by the compound of the invention is believed to be attributable to its strong inhibitory effect against the activated coagulation protease known as Factor Xa. Factor Xa is one of a cascade of proteases involved in the complex process of blood coagulation. The protease known as thrombin is the final protease in the cascade and Factor Xa is the preceding protease which cleaves prothrombin to generate thrombin.

Certain compounds are known to possess Factor Xa inhibitory properties and the field has been reviewed by R.B. Wallis, Current Opinion in Therapeutic Patents, 1993, 1173-1179. Thus it is known that two proteins, one known as antistatin and the other known as tick anticoagulant protein (TAP), are specific Factor Xa inhibitors which possess antithrombotic properties in various animal models of thrombotic disease.

It is also known that certain non-peptidic compounds possess Factor Xa inhibitory properties. Of the low molecular weight inhibitors mentioned in the review by R.B. Wallis, all possessed a strongly basic group such as an amidinophenyl or amidinonaphthyl group.

We have now found that 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl]phenyl}pyridine-1-oxide possesses Factor Xa inhibitory activity.

The compound of the present invention possesses activity in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated, for example in the treatment or prevention of thrombotic conditions such as coronary artery and cerebro-vascular disease. Further examples of such medical disorders include various cardiovascular and cerebrovascular conditions such as myocardial infarction, the formation of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, vascular injury including reocclusion and restenosis following angioplasty and coronary artery bypass surgery, thrombus formation after the application of blood vessel operative techniques or after

general surgery such as hip replacement surgery, the introduction of artificial heart valves or on the recirculation of blood, cerebral infarction, cerebral thrombosis, stroke, cerebral embolism, pulmonary embolism, ischaemia and angina (including unstable angina).

The compound of the invention is also useful as an inhibitor of blood coagulation in an ex-vivo situation such as, for example, the storage of whole blood or other biological samples suspected to contain Factor Xa and in which coagulation is detrimental.

We present as a first feature of the invention the compound of the invention 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl] phenyl} pyridine 1-oxide (hereinafter called the compound of formula I), or a pharmaceutically-acceptable salt thereof or solvate of either thereof.

It is to be understood that the compound of formula I or a pharmaceutically-acceptable salt thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess Factor Xa inhibitory activity.

When a pharmaceutically-acceptable salt of the compound of formula I is required, it may be obtained, for example, by reaction of the compound of formula I with a suitable acid or base using a conventional procedure.

As stated previously, the compound of formula I is an inhibitor of the enzyme Factor Xa. The effects of this inhibition may be demonstrated using one or more of the standard procedures set out hereinafter:-

a) Measurement of Factor Xa Inhibition

An in vitro assay system is carried out based on the method of Kettner et al., J. Biol. Chem., 1990, 265, 18289-18297, whereby various concentrations of a test compound are dissolved in a pH7.5 buffer containing 0.5% of a polyethylene glycol (PEG 6000) and incubated at 37°C with human Factor Xa (0.001 Units/ml, 0.3 ml) for 15 minutes. The chromogenic substrate S-2765 (KabiVitrum AB, 20 μM) is added and the mixture is incubated at 37°C for 20 minutes whilst the absorbance at 405 nm is measured. The maximum reaction velocity (Vmax) is determined and compared with that of a control sample containing no test compound. Inhibitor potency is expressed as an IC_{50} value.

b) Measurement of Thrombin Inhibition

The procedure of method a) is repeated except that human thrombin (0.005 Units/ml) and the chromogenic substrate S-2238 (KabiVitrum AB, 7 μM) are employed.

c) Measurement of Anticoagulant Activity

An in vitro assay whereby human, rat or rabbit venous blood is collected and added directly to a sodium citrate solution (3.2 g/100 ml, 9 parts blood to 1 part citrate solution). Blood plasma is prepared by centrifugation (1000 g, 15 minutes) and stored at 2-4°C. Conventional prothrombin time (PT) tests are carried out in the presence of various concentrations of a test compound and the concentration of test compound required to double the clotting time, hereinafter referred to as CT2, is determined. In the PT test, the test compound and blood plasma are incubated at 37°C for 10 minutes. Tissue thromboplastin with calcium (Sigma Limited, Poole, England) is added and fibrin formation and the time required for a clot to form are determined.

d) An ex vivo Assay of Anticoagulant Activity

The test compound is administered intravenously or orally to a group of Alderley Park Wistar rats. At various times thereafter animals are anaesthetised, blood is collected and PT coagulation assays analogous to those described hereinbefore are conducted.

e) An in vivo Measurement of Antithrombotic Activity

Thrombus formation is induced using an analogous method to that described by Vogel et al., Thromb. Research, 1989, 54, 399-410. A group of Alderley Park Wistar rats is anaesthetised and surgery is performed to expose the vena cava. Collateral veins are ligated and two loose sutures are located, 0.7 cm apart, round the inferior vena cava. Test compound is administered intravenously or orally. At an appropriate time thereafter tissue thromboplastin (30 μl/kg) is administered via the jugular vein and, after 10 seconds, the two sutures are tightened to induce stasis within the ligated portion of vena cava. After 10 minutes the ligated tissue is excised and the thrombus therein is isolated, blotted and weighed.

(f) Rat Disseminated Intravascular Coagulation in vivo activity test

Fasted male Alderley Park rats (300-450 g) are pre-dosed by oral gavage (5 mls/kg) with compound or vehicle (5% DMSO/PEG200) at various times before being anaesthetised with

Intraval® (120 mg/kg i.p.). The left jugular vein and the right carotid artery are exposed and cannulated. A 1 mL blood sample is taken from the carotid canular into 3.2% trisodium citrate. 0.5 mL of the whole blood is then treated with EDTA and used for platelet count determination whilst the remainder is centrifuged (5 mins, 20000g) and the resultant plasma frozen for subsequent drug level, fibrinogen or thrombin antithrombin (TAT) complex determinations. Recombinant human tissue factor (Dade Innovin Cat.B4212-50), reconstituted to the manufacturers specification, is infused (2 mL/kg/hr) into the venous canular for 60 minutes. Immediately after the infusion is stopped a 2 mL blood sample is taken and platelet count, drug level, plasma fibrinogen concentration and TAT complex are determined as before. Platelet counting is performed using at Coulter T540 blood analyser. Plasma fibrinogen and TAT levels are determining using a clotting assay (Sigma Cat.880-B) and TAT ELISA (Behring) respectively. The plasma concentration of the compound is bioassayed using human Factor Xa and a chromogenic substrate S2765 (Kabi), extrapolated from a standard curve (Fragmin) and expressed in Anti-Factor Xa units. The data is analysed as follows; tissue factor-induced reductions in platelet count are normalised with respect to pre-dose platelet count and drug activity expressed as a percent inhibition of tissue factor-induced thrombocytopenia when compared to vehicle treated animals. Compounds are active if there is statistically significant ($p < 0.05$) inhibition of TF-induced thrombocytopenia.

The compound of formula I has an IC_{50} (Factor Xa) of 0.008μM as measured in test a).

According to a further feature of the invention there is provided a pharmaceutical composition which comprises the compound of formula I, or a pharmaceutically-acceptable salt thereof or a solvate of either thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In

general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is the compound of formula I, or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

According to a further feature of the invention there is provided the compound of formula I, or a pharmaceutically-acceptable salt thereof or a solvate of either thereof, for use in medical therapy.

The invention also includes the use of the compound of formula I, or a pharmaceutically-acceptable salt thereof or a solvate of either thereof, in the production of a medicament for use in:-

(i) producing a Factor Xa inhibitory effect;

(ii) producing an anticoagulant effect;

(iii) producing an antithrombotic effect;

(iv) treating a Factor Xa mediated disease or medical condition;

(v) treating a thrombosis mediated disease or medical condition;

(vi) treating coagulation disorders; and/or

(vii) treating thrombosis or embolism involving Factor Xa mediated coagulation.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal requiring such treatment an effective amount of the compound of formula I, or a pharmaceutically-acceptable salt thereof or a solvate of either thereof.

The size of the dose for therapeutic or prophylactic treatment with the compound of formula I, or a pharmaceutically-acceptable salt thereof, will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine. As

mentioned above, the compound of the invention, or a pharmaceutically-acceptable salt thereof, is useful in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated. In using the compound of the invention, or a pharmaceutically-acceptable salt thereof, for such a purpose, it will generally be administered so that a daily dose in the range, for example, 0.5 to 500 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed, for example a dose for intravenous administration in the range, for example, 0.5 to 50 mg/kg body weight will generally be used. For preferred and especially preferred compounds of the invention, in general, lower doses will be employed, for example a daily dose in the range, for example, 0.5 to 10 mg/kg body weight.

Although the compound of formula I, or a pharmaceutically-acceptable salt thereof or a solvate of either thereof, is primarily of value as therapeutic or prophylactic agents for use in warm-blooded animals including man, they are also useful whenever it is required to produce an anticoagulant effect, for example during the ex-vivo storage of whole blood or in the development of biological tests for compounds having anticoagulant properties.

The compound of formula I, or a pharmaceutically-acceptable salt thereof, may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a thrombolytic agent, for example tissue plasminogen activator or derivatives thereof or streptokinase. The compound of formula I may also be administered with, for example, a known platelet aggregation inhibitor (for example aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), a known hypolipidaemic agent or a known anti-hypertensive agent.

The invention will now be illustrated in the following Examples.

Example 1

To a stirred suspension of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine (500mg, 1.04mmol) in dichloromethane (25ml) was added 3-chloroperoxybenzoic acid (640mg of 70-75% strength, 2.6mmol, 2.5mol eq.) and the reaction stirred for 2 hours at ambient temperature, at which time use of thin layer chromatography indicated complete reaction. The reaction mixture was washed sequentially with sodium metabisulphite solution (2x20ml of 1M) and brine, and then dried (phase-separating paper). Evaporation gave crude

product as a brown solid; crystallisation from ethanol gave 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl]phenyl}pyridine-1-oxide as a pale yellow crystalline solid; ^{1}H NMR (d_6-DMSO): 3.0-3.3 (broad s, 4H), 3.4-3.9 (broad d, 4H), 7.0 ppm (s, 1H), 7.35 (d, 1H), 7.5 (m, 3H), 7.8 (m, 5H), 8.3 (d,2H),12.4 (s,1H); MS $(M+H)^+$ 495/497; mp 265-267°C.

The preparation of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine is described in Example 3 of WO99/57113.

Example 2

Illustrative pharmaceutical dosage forms suitable for presenting a compound of formula I, or a pharmaceutically-acceptable salt thereof, for therapeutic or prophylactic use include the following tablet and capsule formulations, which may be obtained by conventional procedures well known in the art of pharmacy and are suitable for therapeutic use in humans:

(a) Tablet I	mg/tablet
Compound Z*	1.0
Lactose Ph. Eur.	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v aqueous paste)	0.75
Magnesium Stearate	1.0

(b) Tablet II	mg/tablet
Compound Z*	50
Lactose Ph. Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

(c) Tablet III	mg/tablet
Compound Z*	100
Lactose Ph. Eur.	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

(d) Capsule	mg/capsule
Compound Z*	10
Lactose Ph. Eur.	488.5
Magnesium stearate	1.5

Note

* The active ingredient Compound Z is a compound of formula I, as described above.

The tablet compositions (a)-(c) may be enteric coated by conventional means, for example, with cellulose acetate phthalate.

Claims

1. 4-{4-[4-(5-Chloroindol-2-ylsulfonyl) piperazine-1-carbonyl] phenyl} pyridine 1-oxide, or a pharmaceutically-acceptable salt thereof or solvate of either thereof.

2. A pharmaceutical composition which comprises 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl] phenyl} pyridine 1-oxide, or a pharmaceutically-acceptable salt thereof or solvate of either thereof, in association with a pharmaceutically-acceptable diluent or carrier.

3. 4-{4-[4-(5-Chloroindol-2-ylsulfonyl) piperazine-1-carbonyl] phenyl} pyridine 1-oxide, or a pharmaceutically-acceptable salt thereof or solvate of either thereof, for use in medical therapy.

4. The use of 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl] phenyl} pyridine 1-oxide, or a pharmaceutically-acceptable salt thereof or solvate of either thereof, in the production of a medicament for use in producing a Factor Xa inhibitory effect.

INTERNATIONAL SEARCH REPORT

Inte .tional Application No
PCT/GB 00/02319

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/50 A61P7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 54164 A (ITO FUMIO ;MORIYA NORIHIKO (JP); TAWADA HIROYUKI (JP); TAKEDA CHEM) 3 December 1998 (1998-12-03) claim 1; examples 47,98 ---	1-4
X	WO 98 21188 A (TURNER PAUL ;PRESTON JOHN (GB); STOCKER ANDREW (GB); ZENECA LTD (G) 22 May 1998 (1998-05-22) page 3, line 30; claims 7-11; examples 4,7,10; table 1 page 7, line 3 ---	1-4
X,P	WO 99 57113 A (CAULKETT PETER WILLIAM RODNEY ;PEARSON STUART ERIC (GB); WALKER RO) 11 November 1999 (1999-11-11) page 6, line 5; example 3 page 6, line 24 - line 27 ---	1-4

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

Inte .ional Application No
PCT/GB 00/02319

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/GB 00/02319

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